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Review article

Combining pharmacotherapy and psychotherapy or monotherapy for major depression? A meta-analysis on the long-term effects

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ABSTRACT

Background: The present meta-analysis aimed to examine to what extent combined pharmacotherapy with psychotherapy results in a different response to treatment compared to psychotherapy or pharmacotherapy alone in adults with major depression at six months or longer postrandomization.
Methods: A systematic literature search resulted in 23 randomized controlled trials with 2184 participants. Combined treatment was compared to either psychotherapy or anti-depressant medication alone in both the acute phase and the maintenance phase. Odds ratios of a positive outcome were calculated for all comparisons.
Results: In acute phase treatment, combined psychotherapy with antidepressants outperformed antidepressants alone at six months or longer postrandomization in patients with major depressive disorder (OR=2.93, 95%CI 2.15–3.99, $p<0.001$). Heterogeneity was zero (95%CI 0–57%, $p>0.05$). However, combined therapy resulted in equal response to treatment compared to psychotherapy alone at six months or longer postrandomization. As for the maintenance treatment, combined maintenance psychotherapy with antidepressants resulted in better-sustained treatment response compared to antidepressants at six months or longer postrandomization (OR=1.61, 95%CI 1.14–2.27, $p<0.05$). Heterogeneity was zero (95%CI 0–68%, $p>0.05$).
Conclusions: Combined therapy results in a superior enduring effect compared to antidepressants alone in patients with major depression. Psychotherapy is an adequate alternative for combined treatment in the acute phase as it is as effective as combined treatment in the long-term.

Contents

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1. Introduction

Depression is a highly prevalent disorder and one of the leading causes of disability worldwide. According to the World Health Organization (WHO), depression is currently the fourth largest contributor to the global burden of disease and is expected to become the second cause of disability by 2020. This is a result of the recurrent nature of depression and its excessive economic costs, mortality, and morbidity rates (Reddy, 2010). Therefore, it is crucial for clinical decision making to identify which therapeutic strategies should be employed to produce the most favorable outcome in the treatment of depression in both the short and the long term.

There is ample evidence for the short-term effects of psychotherapies and pharmacological treatments for depression in the acute (aimed at alleviating the symptoms of an active depression) and the maintenance phase (aimed at preventing future recurrence of the depressive disorder) (Akechi et al., 2008; Beltman et al., 2010; Casacalenda et al., 2002; Cuijpers et al., 2011; Cuijpers and Dekker, 2005; Dennis et al., 2007; Kennedy, 2013; Pizzi et al., 2011; Williams et al., 2000). Meta-analytic studies have shown that, at post-treatment, the effects of psychotherapy and pharmacotherapy in treating mild to moderate depression are comparable (Cuijpers et al., 2013, 2008b), with a combination of pharmacotherapy and psychotherapy showing the best treatment effects when compared to pill placebo, pharmacotherapy and psychotherapy alone (Cuijpers and Dekker, 2005; Cuijpers et al., 2009, 2014, 2012; Khan et al., 2012; Pampallona et al., 2004). However, the long-term effects of the combination of psychotherapy and pharmacotherapy are not well known.

Cuijpers et al. (2009) conducted a meta-analysis to examine the effects of combined psychotherapy with pharmacotherapy versus psychotherapy alone. The authors found no differences in the effects between combined treatment and psychotherapy in the follow up in patients with depression. However, Cuijpers et al. (2009) also included short time intervals in their definition of long-term outcomes, e.g., 1 month follow up (Cuijpers et al., 2009). Thus, an examination focusing specifically on longer follow up periods is warranted. Barber et al. (2013) conducted a systematic review to examine the absolute and relative efficacy of dynamic therapy in treating several mental disorders, such as depression and anxiety. The authors reported that dynamic therapy in combination with pharmacotherapy resulted in significantly higher remission rates compared to pharmacotherapy alone in adults with depression in the long-term (Barber et al., 2013). However, the number of included studies was small ($n=3$) and the results cannot be generalized to other types of psychotherapy. To our knowledge, no systematic review has examined the effects of combined treatment of all major types of psychotherapy and pharmacotherapy against pharmacotherapy alone in adults with major depressive disorder (MDD) in the long term.

Existing treatment guidelines recommend that the provision of antidepressant treatment should last for at least six months in order to prevent recurrence (American Psychiatric Association, 2000). Thus, it is essential to further examine the effects of combined therapy in the long term; such knowledge will provide insight into which therapy we should consider as first line treatment for major depression. The present meta-analysis aimed to examine to what extent combined pharmacotherapy with psychotherapy results in a different response to treatment compared to psychotherapy and pharmacotherapy alone in adults with major depression at six months or longer postrandomization.

2. Methods

This study is based on a more extensive report for the development of treatment guidelines on the long-term effects of psychotherapy on depression (Karyotaki et al., 2014).

2.1. Search strategy

We conducted a systematic literature search in the bibliographic databases of Medline, PsycInfo, Embase and the Cochrane library from database inception to September 1, 2014. Detailed search strategies for PubMed are given in Appendix A. This search strategy was combined with a filter for systematic reviews provided by PubMed (http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html) and a filter for RCTs as recommended in the Cochrane Handbook (Higgins and Green, 2011). Search strategies for other databases were built accordingly.

In addition to the systematic literature search, we checked the references of the selected studies as well as other systematic reviews and meta-analyses in order to identify additional relevant studies. Moreover, we checked an existing database of randomized trials on psychotherapy for depression that has been used by several meta-analyses and is updated yearly (Cuijpers et al., 2008c).

After removal of duplicate publications, two researchers (EK and YS or DB supervised by PC) independently examined titles and abstracts to remove records that were obviously not relevant to the research question according to the guidelines of the Cochrane Handbook (Higgins and Green, 2011). Studies that possibly met inclusion criteria were retrieved full-text and were examined by the same two researchers independently. Any disagreement regarding the inclusion was solved through discussion, and if needed, the opinion of a third researcher (PC) was sought.

2.2. Study selection

We included all main psychotherapy interventions that have been identified in an expert taxonomy of psychotherapy for adult ($\geq$ 18 years of age) depression (Cuijpers et al., 2008a). Here, psychotherapy was classified into seven different types: behavioral activation, cognitive-behavioral therapy, interpersonal therapy, problem solving therapy, psychodynamic therapy, social skills training, and supportive counseling. Operational definitions of each type of psychotherapy are given elsewhere (Cuijpers et al., 2008a, 2008b). We considered for inclusion acute phase treatments as well as maintenance treatments (definitions are given in Table 1) and distinguished these throughout the analyses. The selected interventions were main psychotherapy interventions combined with antidepressive agents compared to main psychotherapy intervention or antidepressants alone.

Table 1
Definitions.

Psychotherapy	Psychotherapy was defined as an intervention in which verbal communication between a therapist and a patient is the core element, or in which a psychological treatment is contained in book format (bibliotherapy) or electronic format (internet-based treatment) that the patient works through more or less independently, but with some kind of personal support from a therapist (guided by telephone, e-mail, or otherwise) (19)
Acute phase treatment	Therapy during the occurrence of depressive symptoms that is targeted at alleviating the symptoms of an active major depressive episode
Maintenance treatment	Therapy in which patients receive maintenance treatment sessions at low frequency rates, for example once monthly, and is aimed at preventing future recurrences of major depressive episode

The primary outcomes of the present meta-analysis were treatment response and sustained response. Treatment response was defined as every positive outcome achieved, such as whether a patient met criteria for remission or was free from relapse or recurrence. Moreover, sustained response was defined as a treatment response that was continued during and after maintenance treatment. Other outcomes were condition-related outcomes (depression rating scales).

Only outcomes at six months or longer after randomization were considered for inclusion. This cut off was chosen because remission is defined as the absence of a depressive disorder three months after the end of therapy, and because anti-depressant medication needs to be provided for at least six months (American Psychiatric Association, 2000). Additionally, a later time point for the cut off did not seem feasible as few studies have a longer follow up period. Outcomes were extracted for different time periods (six months and one year or longer).

2.3. Quality assessment

Two reviewers assessed study quality independently (EK and YS) based on the criteria of the Cochrane Risk of Bias tool (Higgins and Green, 2011). Disagreement was resolved through discussion and, if needed, the opinion of a third researcher (PC) was sought.

2.3.1. Data extraction

The following data were extracted from the included RCTs: patient characteristics, type of psychotherapy, treatment format, number of treatment sessions, type of pharmacotherapy, type of control and data on the follow up period. In some studies, outcome data were only reported for patients who responded to treatment in the acute treatment phase, while others report outcomes for the full, intention-to-treat sample. When available, intention-to-treat data were selected. One reviewer (EK) extracted data; a second reviewer (PC) checked the extracted data.

2.4. Description of the analysis

The primary focus was on dichotomous outcomes. We calculated for each comparison the odds ratio (OR) of a positive outcome, based on dichotomous results, such as remission and response, or the proportion of patients that no longer met criteria for a depressive disorder according to a diagnostic interview. The OR shows the odds that an event (e.g. treatment response) will occur in the treatment group (e.g. combined therapy) compared to the odds of the same event occurring in the control group (e.g. psychotherapy or antidepressants alone). An $OR > 1$ increases the odds that an event will occur in the treatment group. Reversely, an $OR < 1$ decreases the odds that an event will occur in the treatment group (Deeks et al., 2008). Generally, an OR of 1.5 is considered a small effect size, while an OR of 2.5 and OR of 4 represent a medium and a high effect size respectively (Rosenthal, 1996).

Where more than one dichotomous outcome was reported, we calculated the mean of the effect sizes according to Borenstein et al. (2009) procedures. Thus, each comparison resulted in only one effect. If no dichotomous outcomes were reported, the standardized mean difference (SMD) was calculated as the difference in mean scores divided by the pooled standard deviation. The SMD was converted into the OR according to the procedures given by Borenstein et al. (2009). For dichotomous outcomes all randomized patients were taken as the denominator, and reported outcomes in completers were taken as the numerator. To calculate pooled relative risks, we used the computer program Comprehensive Meta-Analysis (version 2.2.021). Because we expected considerable heterogeneity among the studies, we used the random effects model in order to pool the studies.

2.5. Heterogeneity

As a test of homogeneity of effect sizes, the I^2-statistic was calculated which is an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity (Higgins et al., 2003). 95% confidence intervals (CI) were calculated around I^2 (Ioannidis et al., 2007) using the non-central chi-squared-based approach within the heterogi module for Stata (Orsini et al., 2005). The Q-statistic was calculated, and reported when significant.

2.6. Additional analyses

Publication bias was tested by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie (2000) trim and fill procedure (as implemented in Comprehensive Meta-analysis, version 2.2.021). Duval and Tweedie's test estimates the number of missing studies that might exist in a meta-analysis due to publication bias. Trim and fill corrects for the resulting asymmetry in the funnel plot by adjusting the effect size for missing studies (Duval and Tweedie, 2000). Egger's test of the intercept was conducted in order to quantify the bias captured by the funnel plot and test whether it was significant (Egger et al., 1997).

Researcher allegiance for psychotherapy was examined for all the included RCTs. We evaluated a study as at high risk of researcher allegiance when any of the authors was also involved in the development of the treatment manual of the psychotherapy involved. The involvement of a researcher in developing the treatment under investigation is regarded as a valid indicator of researcher allegiance, while the validity of other indicators in reprint measures has been questioned (Munder et al., 2013)

Moderator and subgroup analyses were planned when sufficient studies (at least 3 studies per sub-group) were available.

3. Results

After removal of duplicates, we examined 11145 references on titles and abstracts. This process resulted in 2897 articles being retrieved for possible inclusion in the present meta-analysis. In the 23 RCTs that met inclusion criteria, a total of 2184 individuals suffering from MDD participated in the relevant comparisons combined therapy, psychological and pharmacological interventions. We identified 15 RCTs on acute phase treatment and 8 RCTs on maintenance treatment. Fig. 1 presents the studies selection process.

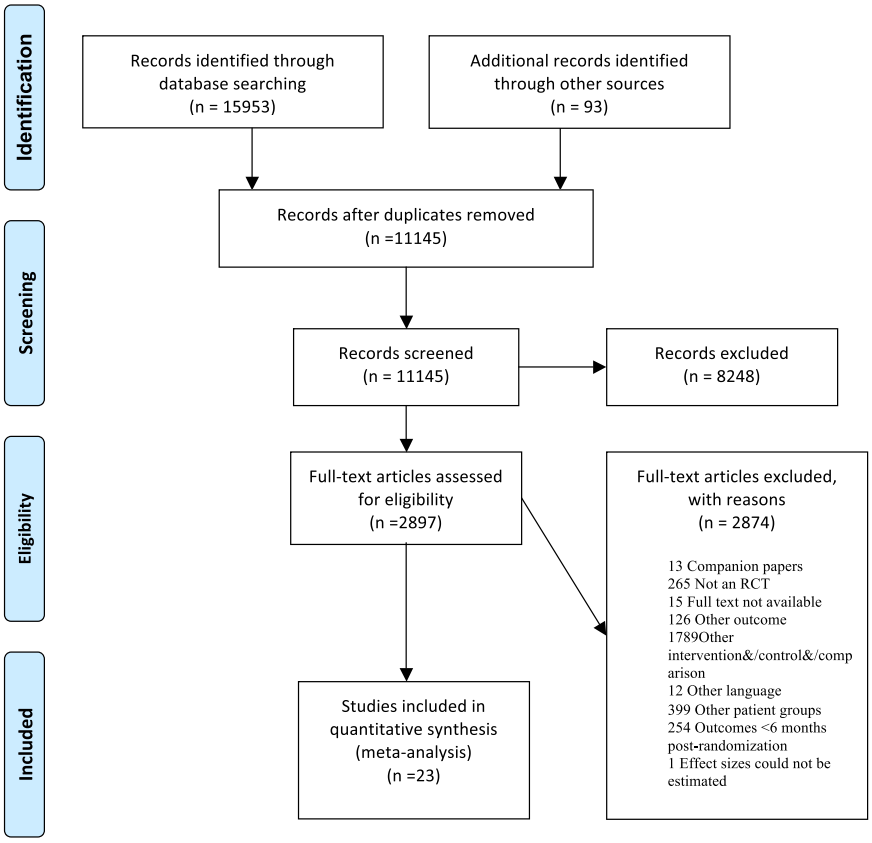

Fig. 1. PRISMA flow chart of the studies inclusion process.

The majority of the included studies recruited their participants through clinical samples, such as general practitioners, outpatient psychiatric clinics and mental health institutes. One RCT recruited patients through both clinical and community referrals, one through community samples, and one did not report the manner of recruitment. Twenty-one of the 23 trials recruited outpatients, while two studies included inpatients. The examined RCTs were conducted across six different countries: Germany ($n=1$), Italy ($n=2$), China ($n=1$), the Netherlands ($n=2$), the United Kingdom ($n=5$) and the United States ($n=12$).

Regarding trials on acute phase treatment, the duration of follow up ranged from six to 48 months after randomization. As for the maintenance studies, patients entered into either maintenance psychotherapy combined with antidepressants or into maintenance antidepressant medication groups and were followed from six to 24 months.

The types of psychotherapy examined across the included trials were: CBT, interpersonal psychotherapy, problem solving therapy, psychodynamic supportive therapy, and social skills training. Acute phase treatment had a duration ranging from six to 29 sessions, while the maintenance psychotherapeutic interventions consisted of six to 20 sessions that were conducted either weekly/biweekly or monthly. The antidepressant agents used were the following: amitriptyline hydrochloride, fluoxetine, fluvoxamine, imipramine hydrochloride, nortriptyline, or sertraline. Study characteristics are given in Table 2.

3.1. Differences between combined psychotherapy and antidepressants vs. psychotherapy alone or antidepressants alone, acute phase treatment

Acute phase combined therapy did not differ significantly in patients' response to treatment, compared to acute phase psychotherapy at six months (OR=1.42, 95%CI 0.97–2.07, $p>0.05$) and one year or longer postrandomization (OR=1.33, 95%CI 0.88–2.14, $p>0.05$). Heterogeneity between studies was zero (95%CI 0–71%, $p>0.05$). There were no indications for publication bias (Table 3). However, combined psychotherapy with antidepressants (acute phase) resulted in a better treatment response compared to acute phase antidepressants after six months or longer post-randomization (OR=2.93, 95%CI 2.15–3.99, $p<0.001$). Heterogeneity between studies was zero (95%CI 0–57%, $p>0.05$). There was some indication of publication bias. Duval and Tweedie's Trim and Fill procedure indicated that two studies were missing. The imputed estimate was 2.71 (95%CI 1.95–3.74). Nevertheless, Egger's Test was not significant ($p>0.05$). Similar results were observed for the same comparisons after one year or longer post-randomization. Combined therapy outperformed antidepressants in treatment response of outpatients with MDD (OR=2.23, 95%CI 1.43–3.41). Heterogeneity was zero (95%CI 0–68%, $p>0.05$). Duval and Tweedie's Trim and Fill procedure indicated a possibility for publication bias and produced an imputed estimate of 1.97 (95%CI 1.29–3.01), however, Egger's test was not significant (Table 4). The main outcomes are summarized in Fig. 2.

3.1.1. Sensitivity and subgroup analyses

Two studies on inpatients were excluded in a sensitivity analysis. Acute phase combined psychotherapy with antidepressants resulted in better response to treatment compared to acute phase antidepressants at six months or longer postrandomization in outpatients with MDD (OR=2.98, 95%CI 2.07–4.29, $p<0.001$). Heterogeneity was low ($I^2=8\%$, 95%CI 0–63%, $p>0.05$). There was some indication of publication bias. Using Trim and Fill the imputed value estimate was 2.80 (95%CI 1.89–4.14) while Egger's test was not significant. A similar pattern of results was observed at one year or longer postrandomization (Table 3). Sub-group

Table 2
Studies characteristics.

Studies	Recruitment	Design	Any AXIS-II Diagnosis (%/ Total N)	PT	*N* patients	Comparison	*N* patients	FU (months)	Outcome	Type of treatment	RA[a]	Risk of bias[b] (0–7)	Country
Beck et al., 1985	CS	RCT	9%	CBT & TCA	15	CBT	18	6, 12	BDI, HRSD	Acute	1	5	US
Bellino et al., 2006	CS	RCT	100%	IPT & SSRI	20	SSRI	19	6	Remission (HRSD scores reduction ≥ 40%)	Acute	0	3	IT
Blackburn et al., 1986	CS	RCT/nat.FU	NR	CBT & TCA	16	TCA CBT	10 15	6, 12, 18, 24	Response (HRSD < 8; BDI < 9)	Acute	0	5	UK
De Jonghe et al., 2001	CS	RCT	NR	PDST & SSRI	83	SSRI	84	6	Remission (HRSD < 8)	Acute	1	4	NL
De Jonghe et al., 2004	CS	RCT	NR	PDST & TCA/SSRI	101	PDST	107	6	Remission (HRSD ≤ 7),	Acute	0	3	NL
Frank et al., 1990	CS	RCT	NR	IPT & TCA	25	TCA	28	12, 24, 36	Recurrence (HRSD ≥ 15); survivors (HRSD < 15; Raskin < 7)	Maintenance	0	4	US
Hersen et al., 1984	Com. S	RCT	NR	SS & TCA	21	TCA	14	6	Depressive symptoms (BDI; HRSD; REDS)	Maintenance	1	4	US
Hollon et al., 1992; Evans, 1992	CS	RCT	NR	CBT & TCA	13	TCA CBT	10 10	24	Relapse (BDI ≥ 16)	Acute	0	4	US
Hollon et al., 2014	CS	RCT	49.8%	CBT & ADM (NS)	187	ADM (NS)	170	12	Recovery (> 26 consecutive weeks without relapse)	Maintenance	0	1	US
Macaskill and Macaskill, 1996	CS	RCT	65%	RET & TCA	10	TCA	10	6	HRSD; BDI	Acute	0	4	UK
Maina et al., 2009	CS	RCT	NR	BDT & SSRI	65	SSRI	83	48	Remission (HRSD ≤ 7)	Acute	0	4	IT
Maina et al., 2010	Com. & CS	RCT	NR	BDT & SSRI	25	SSRI	29	12	Remission (HRSD ≤ 7),	Acute	0	3	IT
Miller et al., 1989	Inpatients	RCT/nat.FU	NR	CBT & TCA	28	TCA	17	6, 12	Remission (HRDS ≤ 7; BDI ≤ 9),	Acute	0	3	US
Mynors-Wallis et al., 2000	CS	RCT	NR	PST & SSRI	35	SSRI PST (GP) PST (nurse)	36 39 41	13	Recovery (HRSD-17 ≤ 7)	Acute	1	1	UK
Paykel et al., 1999	CS	RCT	NR	CBT & TCA	80	TCA	78	17	Relapse (DSM-III-R)	Maintenance	0	3	UK
Perlis et al., 2002	NR	RCT	NR	CBT &SSRI	66	SSRI	66	6	Relapse (HRSD ≥ 15)	Maintenance	0	4	US
Reynolds et al., 1999	NR	RCT	NR	IPT & TCA	16	TCA	25	12	Remission (DSM-IV)	Maintenance	0	4	US
Reynolds et al., 2006	CS	RCT	NR	IPT & SSRI	22	SSRI	24	12	Recurrence (DSM-IV)	Maintenance	1	3	US
Schramm et al., 2007	Inpatients	RCT/nat.FU	21%	IPT & TCA	65	TCA	65	12	Response (HRSD scores reduction ≥ 50%); Recovery (HRSD ≤ 7)	Acute	0	3	DE
Simons et al., 1986	CS	RCT/nat.FU	NR	CBT & TCA	18	TCA CBT	16 19	12	Response (BDI < 10)	Acute	0	4	US
Sirey et al., 2005	CS	RCT	NR	CBT & ADM (NS)	21	ADM (NS)	24	6	Response (HRSD ≤ 10	Acute	1	4	US
Wilkinson et al., 2009	CS	RCT	NR	CBT & SSRI	22	SSRI or TCA	23	6, 12	Recurrence (MADRS ≥ 10; BDI ≥ 12)	Maintenance	1	1	UK
Zu et al., 2014	CS	RCT	NR	CBT SSRI	60	SSRI CBT	60 30	6	Remission QIDS < 5	Acute	0	4	CH

ADM: Antidepressant Medication; BDI: Beck Depression Inventory; BDT: Brief Dynamic Therapy; CBT: Cognitive Behavioral Therapy; CH: China; CIDI: Composite International Clinical Interview; Com. S: Community Sample CS: Clinical Sample; GP: General Practitioner; DE: Germany; DSM: Diagnostic and Statistical Manual of Mental Disorders; FU: Follow Up postrandomization; GP: General Practitioner; HRSD: Hamilton Rating Scale for Depression; IPT: Interpersonal Psychotherapy; IT: Italy; M: month(s); MADRS: Montgomery Asberg Depression Rating Scale; N: number; NL: Netherlands; NR: Not Reported; NS: Not Specified; PDST: Psychodynamic Supportive Therapy; PST: Problem Solving Therapy; PT: Psychotherapy; QIDS:Quick Inventory of Depressive Symptomatology-Self- Report; RA: Research Allegiance; RCT: Randomized Controlled Trial; RCT/nat. FU: Randomized Controlled Trial/Naturalistic Follow Up; SSRI: Selective Serotonin Reuptake Inhibitor; TCA: Tricyclic antidepressant; UK: United Kingdom; US: United States; W: week(s).

[a] One (1) is given when the study was evaluated as at high risk of researcher allegiance and zero (0) when the study was evaluated as at low risk of researcher allegiance.

[b] Sum of 'unclear or high risk of bias' of the individual quality criteria. The sum is derived after assigning a zero (low risk of bias) or one (unclear or high risk of bias) to each one of the following quality criteria: allocation sequence, allocation concealment, blinding of participants and personnel, blinding of assessors, incomplete outcome data, selective reporting, and other sources of bias.

Table 3
Effect sizes for combined psychotherapy and antidepressants vs. psychotherapy in adults with MDD, acute phase.

Outcomes	N	OR	95%CI[a]	I^2	95%CI	p[b]
Response at 6 months or longer postrandomization	8	1.42	0.97–2.07	0	0–68	
Subgroups						
Type of psychotherapy						
CBT vs.	5	1.51	0.79–2.86	0	0–79	0.50
Other	3	1.37	0.85–2.19	0	0–90	
Researcher allegiance						
No	5	1.53	0.97–2.40	0	0–79	0.60
Yes	3	1.19	0.60–2.40	0	0–90	
Response at 1 year or longer postrandomization	7	1.33	0.88–2.14	0	0–71	
Subgroups						
Type of psychotherapy						
CBT vs.	4	1.48	0.59–3.71	0	0–85	0.80
Other	3	1.24	0.68–2.22	0	0–90	
Researcher allegiance						
No	4	1.36	0.82–2.25	0	0–85	0.90
Yes	3	1.28	0.64–2.58	0	0–90	

Subgroup analyses were conducted only in the cases where at least three comparisons were available per group. *N*: Number of comparisons.

[a] 95%CI: 95% Confidence Intervals; OR: Odds Ratio; *p*: *p*-value.

[b] *p*-value between groups.

Table 4
Effect sizes for combined psychotherapy with antidepressants vs. antidepressants in adults with MDD, acute phase.

Outcomes	N	OR	95%CI[a]	I^2	95%CI	p[b]
Response at 6 months or longer postrandomization	13	2.93*	2.15–3.99	0	0–57	
Subgroups						
Type of psychotherapy						
CBT vs.	6	3.02*	1.74–5.25	0	0–75	0.88
Other	7	2.87*	1.77–4.64	32	0–71	
Risk of bias						
Risk of bias ≤ 3vs.	4	1.66	0.98–2.81	0	0–85	0.17
Risk of bias >3	5	2.26*	1.35–3.78	13	0–82	
Types of antidepressants						
SSRI	6	2.64*	1.70–4.11	19	0–64	0.51
TCA	6	3.37*	1.90–5.99	0	0–75	
Response at 1 year or longer postrandomization	8	2.23*	1.43–3.41	0	0–68	
Subgroups						
Type of psychotherapy						
CBT vs.	4	3.37*	1.38–8.21	0	0–85	0.29
Other	4	1.94*	1.16–3.23	0	0–85	
Risk of bias						
Risk of bias ≤ 3 vs.	4	1.94*	1.16–3.23	0	0–85	0.29
Risk of bias >3	4	3.37*	1.38–8.21	0	0–85	
Types of antidepressants						
SSRI	3	1.64	0.84–3.18	0	0–90	0.22
TCA	5	2.84	1.57–5.16	0	0–79	
Sensitivity analysis						
Response at 6 months or longer postrandomization (inpatients excluded)	11	2.98*	2.07–4.29	8	0–63	
Response at 1 year or longer postrandomization (inpatients excluded)	6	1.99*	1.14–3.47	0	0–75	

Subgroup analyses were conducted only in the cases where at least three comparisons were available per group. *N*: Number of comparisons.

* $p < 0.05$.

[a] 95%CI: 95% Confidence Intervals; OR: Odds Ratio; *p*: *p*-value.

[b] *p*-value between groups.

analyses (high vs. low quality studies; CBT vs. other types of therapy; researcher allegiance vs. no researcher allegiance for psychotherapy) did not result in statistically significant differences (Table 4).

3.2. Differences between combined psychotherapy with antidepressants vs. psychotherapy alone or antidepressants alone in adults who have had MDD, maintenance treatment

Only one study (Frank et al. 1990) examined the comparison between combined maintenance psychotherapy with antidepressants and maintenance psychotherapy at six months or longer post-randomization. Thus, we could not examine this comparison.

Table 5 shows the results of the comparison between maintenance combined psychotherapy and antidepressants at six months or longer postrandomization. Combined maintenance psychotherapy with antidepressants resulted in a better treatment-sustained response compared to antidepressants at six months or longer postrandomization (OR=1.61, 95%CI 1.14–2.27, $p < 0.05$). Heterogeneity was zero (95%CI 0–68%, $p < 0.05$). There was no indication of publication bias. Six studies compared the outcomes of combined maintenance psychotherapy with antidepressants versus antidepressants at one year or longer postrandomization. Combined maintenance psychotherapy with antidepressants resulted in a better-sustained response to treatment in comparison with antidepressants (OR=1.73, 95%CI 1.20–2.49, $p < 0.05$) after one year or longer postrandomization. Heterogeneity between the studies was zero (95%CI 0–75%, $p > 0.05$). There was no indication of publication bias. Finally, subgroup analyses (studies with high vs. studies with low risk of bias, CBT vs. other types of therapy, SSRI vs. TCA antidepressants, and researcher allegiance vs. no researcher allegiance for psychotherapy) did not result in statistically significant differences.

The main outcomes of our analyses are summarized in Fig. 2. The forest plots of the main outcomes can be found in Appendix B.

4. Discussion

The aim of the present meta-analysis was to examine to what extent combined pharmacotherapy with psychotherapy results in a different long-term response to treatment compared to psychotherapy and pharmacotherapy alone in adults with major depression. Results indicated that combined psychotherapy with antidepressants resulted in an equal acute phase treatment response compared to psychotherapy at six months or longer postrandomization, in adult patients with MDD. Further, combined psychotherapy with antidepressants resulted in a better acute phase treatment response compared to antidepressants alone, at six months or longer postrandomization. As for the maintenance studies, there was evidence that maintenance-combined psychotherapy with antidepressants resulted in a better-sustained response compared to maintenance antidepressants alone, at six months or longer postrandomization.

The results of the comparison between combined therapies versus antidepressants alone (acute phase treatment) may have been somewhat overestimated due to publication bias. This indication of publication bias is in accordance with previous meta-analyses on the same comparison (Cuijpers et al., 2014). However, the point estimate remained high and significant after the adjustment for publication bias.

The results of the present meta-analysis are in line with previous research, which compared the effects of combined therapy against antidepressants in patients with depression and anxiety disorders in the short term (Cuijpers and Dekker, 2005; Cuijpers et al., 2009, 2014, 2012; Khan et al., 2012; Pampallona et al., 2004). A recent meta-analysis by Cuijpers et al. (2014) showed that adding psychotherapy to antidepressants results in overall superior short-term effects compared to antidepressants alone in patients with MDD, panic disorder and obsessive compulsive

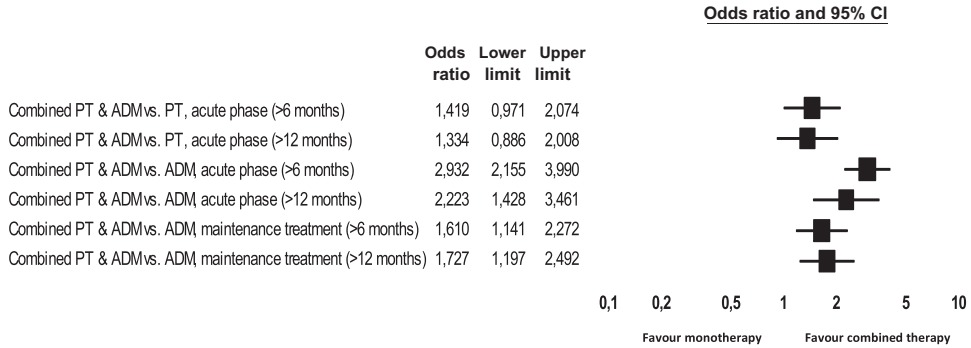

Fig. 2. Main outcomes of combined psychotherapy and antidepressant medications (PT&ADM) in Odds ratio (OR) and 95% Confidence intervals (95%CI).

Table 5
Effect sizes maintenance psychotherapy with antidepressants vs. antidepressants in adults with MDD.

Outcomes	*N*	OR	95%CI[a]	I^2	95%CI	*p*[b]
Sustained response at 6 months or longer postrandomization	8	1.61*	1.14–2.27	0	0–68	
Subgroups						
Type of psychotherapy						
CBT vs.	4	1.79*	1.19–2.70	0	0–85	0.32
Other	4	1.23	0.64–2.33	0	0–85	
Risk of bias						
Risk of bias ≤ 3	5	1.75*	1.20–2.56	0	0–79	0.28
Risk of bias > 3	3	1.07	0.47–2.45	0	0–90	
Researcher allegiance						
No	5	1.80*	1.21–2.65	0	0–79	0.26
Yes	3	1.12	0.55–2.30	0	0–90	
Types of antidepressants						
SSRI	3	1.26	0.60–2.64	0	0–90	0.43
TCA	4	1.81*	1.08–3.03	0	0–85	
Sustained response at 1 year or longer postrandomization	6	1.73*	1.20–2.49	0	0–75	

Subgroup analyses were conducted only in the cases where at least three comparisons were available per group. *N*: Number of comparisons.

* $p < 0.05$.

[a] 95%CI: 95% Confidence Intervals; OR: Odds Ratio; *p*: *p*-value.

[b] *p*-value between groups.

disorder. The authors also reported that these effects were sustained during 2 years follow-up (Cuijpers et al., 2014). The present findings are also in line with the results of Barber et al. (2013) on dynamic therapy. The authors found that in the long-term dynamic therapy combined with antidepressants results in higher remission rates compared to antidepressants alone in adults with depression (Barber et al., 2013). Moreover, the finding that acute phase combined therapy results in no differences in treatment response compared to acute psychotherapy in longer than 6 months post-randomization is in accordance with Cuijpers et al. (2009) meta-analysis. Cuijpers et al. (2009) showed that there are no differences between the effects of combined therapy and psychotherapy at longer than 1 month follow up in patients with depression (Cuijpers et al., 2009). To the best of our knowledge there is no systematic review examining the effects of maintenance combined therapy.

The present study has several strengths. The included studies targeted outpatients with MDD and thus, the results of the present review refer to a highly homogeneous population. Additionally, our results are based on a direct comparison between acute/maintenance phase combined treatment and acute phase antidepressants/psychotherapy or maintenance antidepressants.

However, the present results should be interpreted with caution due to several limitations. Most of the included trials used CBT as a psychotherapeutic intervention, therefore, differences between different types of psychotherapy could not be examined and the generalizability of the present findings to all types of psychotherapy is restricted. Similarly, a distinction between depression severities was not possible because there were no specific studies with a distinction between mild, moderate and severe MDD. The outcome was specified to treatment response since the included studies did not provide enough information on outcomes assessed by clinical interview. Furthermore, we identified only one trial on the comparison between maintenance combined therapy and psychotherapy alone (Frank et al., 1990). Thus, we could not analyze this comparison and we limited our analysis to the comparison between maintenance-combined therapy against maintenance antidepressants. Finally, a limitation that should be acknowledged is that the sample at randomization is typically not the same as the one at long-term follow-up, in spite of using advanced statistics to model missing data.

With respect to researcher allegiance, a bias of concern in psychotherapy research (Munder et al., 2013), we did not find evidence that studies at a high risk of researcher allegiance for psychotherapy favored psychotherapy more than did studies at a low risk of researcher bias. However, the number of studies in each subgroup was small, and we did not examine more subtle forms of researcher allegiance for psychotherapy such as whether authors advocated the psychotherapy or the mix of research teams (including methodologists and/or psychiatrists). As for our own researcher allegiance, we have carried out in the past a series of meta-analyses of several different types of psychotherapy and pharmacotherapy and we do not prefer one treatment to another. Additionally, we believe that out team is well balanced as it consists of researchers in clinical psychology as well as experts in evidence-based medicine.

The results of this meta-analysis raise several clinical possibilities. Currently, antidepressants are widely used as first option in treating major depression in primary and secondary mental health care (Geddes et al., 2003). Given the high risk of relapse (Keller, 1994), alternative treatment options should also be proposed. The present findings highlight that the combination of psychotherapy with antidepressants provides clinical gains in terms of long-term sustainability of the treatment response. Thus, in light of the enduring effects, combined therapy may be preferred over monotherapy with antidepressants in treatment of major depression.

However, while combined therapy enhanced response rates relative to antidepressant alone, the present results failed to demonstrate a superiority of combined treatment compared to psychotherapy alone, after acute phase treatment. This might be due to the limited number of trials on the comparison between combined therapy and psychotherapy alone and it remains to be confirmed by future studies. However, it could also indicate that psychotherapy is in fact a viable alternative for combined treatment, which is important to note for several reasons. Psychotherapy in contrast to medication is not related to side effects (National Collaborating Centre for Mental Health, 2010) and

teaches patients a set of skills and coping mechanisms, which they can employ and use to sustain their improvement after the treatment phase is over. Furthermore, in evidence based practice the decision-making is based on both treatment effectiveness and patient preferences. Considering that combined therapy and psychotherapy alone result in equivalent outcomes over the long-term, patients' preferences is an important factor when choosing treatment modality. Previous research has shown that some patients prefer psychotherapy to taking medication (van Schaik et al., 2004); thus, access to both psychotherapy and pharmacotherapy in primary and secondary mental health care may increase the chance of patients following their preferred treatment (Winter and Barber, 2013).

Further research is warranted to address outcomes such as quality of life or adverse events, and to examine more types of psychotherapy. To conclude, the present results suggest that combined treatment is the best available option both as acute and as maintenance therapy for treating major depression in the long term. In addition, if a patient does not prefer the combined treatment, acute phase psychotherapy could also be a treatment option as it is as effective as acute phase combined treatment in the long term.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.01.036.

References

Akechi, T., Okuyama, T., Onishi, J., Morita, T., Furukawa Toshi, A., 2008. Psychotherapy for depression among incurable cancer patients. Cochrane Database Syst. Rev.

American Psychiatric Association, 2000. Practice guideline for the treatment of patients with major depressive disorder (revision). Am. J. Psychiatry 157, 1–45.

Barber, J.P., Muran, J.C., McCarthy, K.S., Keefe, R., 2013. Research on psychodynamic therapies. In: Lambert, M.J. (Ed.), Bergin and Garfield's Handbook of Psychotherapy and Behavior Change. John Wiley & Sons, Inc, New-York, NY, pp. 443–494.

Beck, A.T., Hollon, S.D., Young, J.E., Bedrosian, R.C., Budenz, D. Treatment of depression with cognitive therapy and amitriptyline. Arch Gen Psychiatry 42, 1985, 142-148.

Beltman, M.W., Voshaar, R.C.O., Speckens, A.E., 2010. Cognitive–behavioural therapy for depression in people with a somatic disease: meta-analysis of randomised controlled trials. Br. J. Psychiatry 197, 11–19.

Bellino, S., Zizza, M., Rinaldi, C., Bogetto, F. Combined treatment of major depression in patients with borderline personality disorder: a comparison with pharmacotherapy. Can J Psychiatry 51, 2006, 453-460.

Blackburn, I.M., Eunson, K.M., Bishop, S., 1986. A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. J. Affect. Disord. 10, 67–75.

Borenstein M., Hedges L.V., Higgins J.P.T. and Rothstein H.R.,Introduction to Meta-Analysis. Chichester, UK, 2009, Wiley.

Casacalenda, N., Perry, J.C., Looper, K., 2002. Remission in major depressive disorder: a comparison of pharmacotherapy, psychotherapy, and control conditions. Am. J. Psychiatry 159, 1354–1360.

Cuijpers, P., Andersson, G., Donker, T., van Straten, A., 2011. Psychological treatment of depression: results of a series of meta-analyses. Nord. J. Psychiatry 65, 354–364.

Cuijpers, P., Dekker, J., 2005. Psychological treatment of depression; a systematic review of meta-analyses. Ned. Tijdschr. voor Geneeskd. 149, 1892–1897.

Cuijpers, P., Dekker, J., Hollon, S.D., Andersson, G., 2009. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis. J. Clin. Psychiatry 70, 1219–1229.

Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S.D., van Straten, A., 2014. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. J. Affect. Disord. 159, 118–126.

Cuijpers, P., Reynolds, C.F., Donker, T., Li, J., Andersson, G., Beekman, A., 2012. Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. Depression Anxiety 29, 855–864.

Cuijpers, P., Sijbrandij, M., Koole, S.L., Andersson, G., Beekman, A.T., Reynolds 3rd, C. F., 2013. The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. World Psychiatry 12, 137–148.

Cuijpers, P., van Straten, A., Andersson, G., van Oppen, P., 2008a. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. J. Consult. clin. Psychol. 76, 909–922.

Cuijpers, P., van Straten, A., van Oppen, P., Andersson, G., 2008b. Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? A meta-analysis of comparative studies. J. Clin. Psychiatry 69, 1675–1685, quiz 1839-1641.

Cuijpers, P., van Straten, A., Warmerdam, L., Andersson, G., 2008c. Psychological treatment of depression: a meta-analytic database of randomized studies. BMC Psychiatry 8, 36.

Cuijpers, P., van Straten, A., Warmerdam, L., Andersson, G., 2009. Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: a meta-analysis. Depression Anxiety 26, 279–288.

Deeks, J.J., Higgins, J., Altman, D.G., 2008. Analysing data and undertaking meta-analyses, Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series, pp. 243–296.

de Jonghe, F., Hendricksen, M., van Aalst, G., Kool, S., Peen, V., Van, R., van den Eijnden, E., Dekker, J. Psychotherapy alone and combined with pharmacotherapy in the treatment of depression. Br J Psychiatry 185, 2004, 37-45.

de Jonghe, F., Kool, S., van Aalst, G., Dekker, J., Peen, J. Combining psychotherapy and antidepressants in the treatment of depression. J Affect Disord 64, 2001, 217-229.

Dennis, C.L., Ross, L.E., Grigoriadis, S., 2007. Psychosocial and psychological interventions for treating antenatal depression. Cochrane Database Syst. Rev., CD006309.

Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455–463.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.

Evans, M.D., Hollon, S.D., DeRubeis, R.J., Piasecki, J.M., Grove, W.M., Garvey, M.J., Tuason, V.B. Differential relapse following cognitive therapy and pharmacotherapy for depression. Arch Gen Psychiatry 49, 1992, 802-808.

Frank, E., Kupfer, D.J., Perel, J.M., Cornes, C., Jarrett, D.B., Mallinger, A.G., Thase, M.E., McEachran, A.B., Grochocinski, V.J., 1990. Three-year outcomes for maintenance therapies in recurrent depression. Arch. Gen. Psychiatry 47, 1093–1099.

Geddes, J.R., Carney, S.M., Davies, C., Furukawa, T.A., Kupfer, D.J., Frank, E., Goodwin, G.M., 2003. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 361, 653–661.

Hersen, M., Bellack, A.S., Himmelhoch, J.M., Thase, M.E., 1984. Effects of social skill training, amitriptyline, and psychotherapy in unipolar depressed women. Behav. Ther. 15, 21–40.

Higgins, J., Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions : Version 5.1.0, The Cochrane collaboration, Updated March 2011.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560.

Hollon, S.D., DeRubeis, R.J., Evans, M.D., Wiemer, M.J., Garvey, M.J., Grove, W.M., Tuason, V.B., 1992. Cognitive therapy and pharmacotherapy for depression. Singly and in combination. Arch. Gen. Psychiatry 49, 774–781.

Hollon, S.D., DeRubeis, R.J., Fawcett, J., Amsterdam, J.D., Shelton, R.C., Zajecka, J., Young, P.R., Gallop, R. Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial. JAMA psychiatry 71, 2014, 1157-1164.

Ioannidis, J.P., Patsopoulos, N.A., Evangelou, E., 2007. Uncertainty in heterogeneity estimates in meta-analyses. BMJ 335, 914–916.

Karyotaki, E., Smit, Y., Cuijpers, P., Gillain, B., Fairon, N., Paulus, D., Robays, J., Holdt Henningsen, K. Major Depression: Long term efficacy of psychotherapy, alone or in combination with antidepressants, 2014, KCE Reports.

Keller, M.B., 1994. Depression: a long-term illness. Br. J. Psychiatry.

Kennedy, S.H., 2013. A review of antidepressant therapy in primary care: current practices and future directions. Prim. Care Companion J. Clin. Psychiatry, 15.

Khan, A., Faucett, J., Lichtenberg, P., Kirsch, I., Brown, W.A., 2012. A systematic review of comparative efficacy of treatments and controls for depression. PloS One 7, e41778.

Macaskill, N.D., Macaskill, A., 1996. Rational-emotive therapy plus pharmacotherapy versus pharmacotherapy alone in the treatment of high cognitive dysfunction depression. Cogn. Ther. Res. 20, 575–592.

Maina, G., Rosso, G., Bogetto, F., 2009. Brief dynamic therapy combined with pharmacotherapy in the treatment of major depressive disorder: long-term results. J. Affect. Disord. 114, 200–207.

Maina, G., Rosso, G., Rigardetto, S., Piat, S.C., Bogetto, F., 2010. No effect of adding brief dynamic therapy to pharmacotherapy in the treatment of obsessive-compulsive disorder with concurrent major depression. Psychother. Psychosom. 79, 295–302.

Miller, I.W., Norman, W.H., Keitner, G.I., 1989. Cognitive-behavioral treatment of depressed inpatients: six- and twelve-month follow-up. Am. J. Psychiatry 146, 1274–1279.

Munder, T., Brütsch, O., Leonhart, R., Gerger, H., Barth, J., 2013. Researcher allegiance in psychotherapy outcome research: an overview of reviews. Clin. Psychol. Rev. 33, 501–511.

Mynors-Wallis, L.M., Gath, D.H., Day, A., Baker, F. Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. Bmj 320, 2000, 26-30.

National Collaborating Centre for Mental Health, 2010. Depression: the treatment and management of depression in adults (updated edition). Br. Psychol. Soc.

Orsini, N., Bottai, M., Higgins, J., Buchan, L., 2005. HETEROGI: Stata module to quantify heterogeneity in a meta-analysis.

Pampallona, S., Bollini, P., Tibaldi, G., Kupelnick, B., Munizza, C., 2004. Combined pharmacotherapy and psychological treatment for depression: a systematic review. Arch. Gen. Psychiatry 61, 714–719.

Paykel, E.S., Scott, J., Teasdale, J.D., Johnson, A.L., Garland, A., Moore, R., Jenaway, A., Cornwall, P.L., Hayhurst, H., Abbott, R., Pope, M. Prevention of relapse in residual depression by cognitive therapy: a controlled trial. Arch Gen Psychiatry 49, 1999, 829-835.

Perlis, R.H., Nierenberg, A.A., Alpert, J.E., Pava, J., Matthews, J.D., Buchin, J., Sickinger, A.H., Fava, M. Effects of adding cognitive therapy to fluoxetine dose increase on risk of relapse and residual depressive symptoms in continuation treatment of major depressive disorder J Clin Psychopharmacol 22, 2002, 474-480.

Pizzi, C., Rutjes, A.W.S., Costa, G.M., Fontana, F., Mezzetti, A., Manzoli, L., 2011. Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. Am. J. Cardiol. 107, 972–979.

Reddy, M.S., 2010. Depression: the disorder and the burden. Indian J. Psychol. Med. 32, 1–2.

Reynolds 3rd, C.F., Frank, E., Dew, M.A., Houck, P.R., Miller, M., Mazumdar, S., Perel, J.M., Kupfer, D.J., 1999. Treatment of 70(+)-year-olds with recurrent major depression. Excellent short-term but brittle long-term response. Am. J. Geriatr. Psychiatry 7, 64–69.

Reynolds III, C.F., Dew, M.A., Pollock, B.G., Mulsant, B.H., Frank, E., Miller, M.D., Houck, P.R., Mazumdar, S., Butters, M.A., Stack, J.A., Schlernitzauer, M.A., Whyte, E.M., Gildengers, A., Karp, J., Lenze, E., Szanto, K., Bensasi, S., Kupfer, D.J. Maintenance treatment of major depression in old age New England Journal of Medicine 354, 2006, 1130-1138.

Rosenthal, J.A., 1996. Qualitative descriptors of strength of association and effect size. J. Soc. Serv. Res. 21, 37–59.

Schramm, E., van Calker, D., Dykierek, P., Lieb, K., Kech, S., Zobel, I., Leonhart, R., Berger, M., 2007. An intensive treatment program of interpersonal psychotherapy plus pharmacotherapy for depressed inpatients: acute and long-term results. Am. J. Psychiatry 164, 768–777.

Simons, A.D., Murphy, G.E., Levine, J.L., Wetzel, R.D., 1986. Cognitive therapy and pharmacotherapy for depression. Sustained improvement over one year. Arch. Gen. Psychiatry 43, 43–48.

Sirey, J.A., Bruce, M.L., Alexopoulos, G.S., 2005. The Treatment Initiation Program: an intervention to improve depression outcomes in older adults. Am. J. Psychiatry.

van Schaik, D.J., Klijn, A.F., van Hout, H.P., van Marwijk, H.W., Beekman, A.T., de Haan, M., van Dyck, R., 2004. Patients' preferences in the treatment of depressive disorder in primary care. Gen. Hosp. Psychiatry 26, 184–189.

Wilkinson, P., Alder, N., Juszczak, E., Matthews, H., Merritt, C., Montgomery, H., Howard, R., Macdonald, A., Jacoby, R. A pilot randomised controlled trial of a brief cognitive behavioural group intervention to reduce recurrence rates in late life depression. Int J Geriatr Psychiatry 24, 2009, 68-75.

Williams Jr., J.W., Mulrow, C.D., Chiquette, E., Noel, P.H., Aguilar, C., Cornell, J., 2000. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Ann. Intern. Med. 132, 743–756.

Winter, S.E., Barber, J.P., 2013. Should treatment for depression be based more on patient preference? Patient Preference Adherence 7, 1047.

Zu, S., Xiang, Y.-T., Liu, J., Zhang, L., Wang, G., Ma, X., Kilbourne, A.M., Ungvari, G.S., Chiu, H.F., Lai, K.Y., 2014. A comparison of cognitive-behavioral therapy, antidepressants, their combination and standard treatment for Chinese patients with moderate–severe major depressive disorders. J. Affect. Disord. 152, 262–267.